Stem Cell Metabolism

In stem cells, the metabolic pathways appear to play a crucial role in balancing stem cell maintenance and differentiation.

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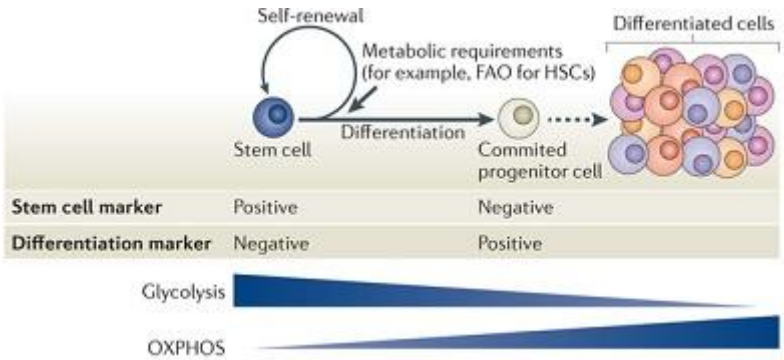
Stem cells are unspecialized cells that have the ability to replicate themselves and to repair and replace specific tissues in the body by developing into mature cells. Two major types of stem cells can be distinguished: embryonic stem cells, which can differentiate into all types of specialized cells, and lineage-restricted adult stem cells. The ability of stem cells to replicate themselves, a process known as self-renewal, is essential for expansion of stem cell numbers during embryonic development and for maintenance of the stem cell pool throughout adult life. Reduced self-renewal, resulting in differentiation, will eventually lead to exhaustion of the stem cell pool and impaired tissue repair. In addition, tissue stem cells or early progenitors that undergo mutations that enhance the normal self-renewal capacity, induce proliferation and impair development will convert into cancer stem cells and initiate tumour formation. Tight regulation of these processes is therefore essential. Although all cells in the body rely on metabolism for their energy supply, stem cells and mature cells use different metabolic pathways to produce energy.

Anaerobic glycolysis in stem cells

Every process in a cell requires energy. Most cells use the same energy source, the rechargeable energy carrier, adenosine triphosphate (ATP). In eukaryotes, ATP is usually produced by aerobic glycolysis in mitochondria. This process, which is also known as oxidative phosphorylation, requires oxygen. If necessary, cells can adapt to low-oxygen conditions by producing ATP in an oxygen-independent manner. This process is activated by Hypoxia-inducible factors (HIF). These factors can transcriptionally activate genes involved in anaerobic glycolysis. Although anaerobic glycolysis allows cells to survive under low oxygen conditions, this process is not as efficient as oxidative phosphorylation.



In contrast to mature cells, stem cells usually reside in specialized microenvironments with a low oxygen tension. This low oxygen concentration is thought to keep stem cells in a slowly dividing and undifferentiated state. Supplementing different types of adult stem cells, including Hematopoietic stem cells (HSCs), Mesenchymal Stem Cells (MSCs) and Neural Stem Cells (NSCs) with oxygen results in enhanced proliferation. Due to the low oxygen levels in their microenvironment, both embryonic and adult stem cells primarily rely on anaerobic glycolysis for their energy supply. Embryonic stem cells contain

functionally immature mitochondria, further indicating that, in these cells, mitochondria do not play an important role in ATP production. Similarly, mitochondria in HSCs are relatively inactive.

The use of anaerobic glycolysis for ATP production is not only a mere consequence of low oxygen tension, but appears to be important for maintenance of both embryonic and adult stem cells. It has, for example, been shown that hypoxia-induced stimulation of anaerobic glycolysis promotes pluripotency in embryonic stem cells, while inhibition of glycolysis impairs their stem cell capacities. Similarly, induction of oxidative phosphorylation, by depletion of HIF1 or its downstream effectors, leads to exhaustion of HSCs.

Reactive oxygen species and stem cell maintenance

Reactive oxygen species are generally considered to be toxic by-products of oxidative phosphorylation. Since high levels of ROS can impair cellular processes by damaging lipids, proteins, RNA and DNA, cells need to minimize their ROS levels. This is of particular importance for stem cells that have to ensure life-long tissue renewal. A high level of intracellular ROS is sufficient to diminish the self-renewal capacity of adult stem cells, resulting in either differentiation or apoptosis. A hypoxic environment in which stem cells are maintained in a slowly cycling manner is thought to protect stem cells from the detrimental accumulation of ROS. In addition, stem cells can minimize ROS levels by using anaerobic glycolysis for their energy supply. However, acute hypoxia has been shown to increase the level of intracellular ROS in adipose derived stem cells.

This suggests that stem cells may utilize additional mechanisms to actively reduce intracellular ROS levels. Indeed, a system of antioxidant enzymes, such as superoxide dismutases and catalases can convert intracellular ROS to H_2O_2 and eventually H_2O. The activity of these enzymes can be regulated by transcription factors known to play an important role in stem cell maintenance such as Nrf2 and members of the FoxO family. Although ROS levels have to be low for normal stem cell maintenance, specific situations, such as bone marrow injury, require high ROS levels to induce proliferation and differentiation and restore homeostasis.

Induction of oxidative phosphorylation during differentiation

The mitochondria of embryonic stem cells undergo significant maturation changes during differentiation. Intermediates of the oxidative phosphorylation pathway are up-regulated simultaneously, allowing a switch from anaerobic glycolysis to oxidative phosphorylation in the mitochondria. This transition to oxidative phosphorylation results in a more efficient energy supply, which is necessary for normal development of these cells.

A similar shift has been observed during the development of various types of adult stem cells, including HSCs and NSCs. Differentiation of these lineages appears to depend on the presence of oxidative phosphorylation and an increase in ROS levels. However, this switch in metabolic pathways does not appear to be a universal phenomenon. MSCs can give rise to a variety of tissues, including bone, cartilage, muscle, adipose, and stroma. The development of some of these mesenchymal tissues requires a further reduction in oxidative phosphorylation in favor of anaerobic glycolysis. In addition, other mesenchymal progenitors actively up-regulate antioxidant enzymes to prevent accumulation of ROS during differentiation, indicating that the mitochondria-induced increase in ROS levels is not beneficial for all differentiating progenitors.

Although all cells rely on metabolism for their energy supply, in stem cells, the metabolic pathways appear to play a crucial role in balancing stem cell maintenance and differentiation. A complete understanding of the underlying mechanisms will not only provide important insights into this relationship, but may also contribute to the

development of novel therapeutic strategies for patients with cancer or other life-threatening illnesses in which tissue generation is disturbed. Most cancer cells, for example, exhibit increased glycolysis. This appears to be due to defects in mitochondria, abnormal expression of metabolic enzymes and the low oxygen tension in the tumor microenvironment. This increased dependence of cancer cells on glycolytic pathways allows the development of small molecules that preferentially kill cancer cells by pharmacological inhibition of glycolysis. In addition, hematopoietic stem cell transplantation is an important therapeutic means for patients with cancer in the bone marrow.

Understanding the role of metabolic pathways in HSC maintenance and differentiation will help develop novel methods to expand HSCs before transplantation and to accelerate outgrowth of mature cells after transplantation. This would significantly improve the clinical outcome of this procedure. Furthermore, cells from patients with serious illnesses in which tissue generation or function is disturbed can be converted to a pluripotent state (iPS), modulated and then forced to develop into those tissue cells that were absent or malfunctioning due to the disease. Modulation of metabolism during this procedure may aid both the conversion to iPS and the targeted differentiation to mature cells, resulting in a higher levels of iPS cells and more efficient regeneration of tissue.